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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/806,611	03/22/2004	Mary Collins	01997.043200	2470

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EXAMINER	
WANG, CHANG YU	

ART UNIT	PAPER NUMBER
1649	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Advisory Action Before the Filing of an Appeal Brief	**Application No.** 10/806,611	**Applicant(s)** COLLINS ET AL.	
	Examiner Chang-Yu Wang	**Art Unit** 1649	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 11 February 2008 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☐ The period for reply expires _____months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☒ The Notice of Appeal was filed on *2/11/08*. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☒ Applicant's reply has overcome the following rejection(s): See Continuation Sheet.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: *1,3-15,17-19,29-36 and 38-40*.
   Claim(s) withdrawn from consideration: *20-28 and 41-49*.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because:
    See Continuation Sheet.
12. ☐ Note the attached Information *Disclosure Statement*(s). (PTO/SB/08) Paper No(s). _____
13. ☐ Other: _____.

/C. Y. W./
Examiner, Art Unit 1649

/Christine J Saoud/
Primary Examiner, Art Unit 1647

Continuation of 5. Applicant's reply has overcome the following rejection(s): the rejection of claims 1-19 and 29-40 under 35 U.S.C. 112, first paragraph, for failing to comply with the written description requirement due to new matter and the rejection under 112-2nd paragraph, indefiniteness due to new matter.

Continuation of 11. does NOT place the application in condition for allowance because: Applicant's arguments have been fully considered but they are insufficient to overcome the rejections under 112-1st paragragph, lack of scope of enablment and written description requirement, the rejection under 112-2nd paragraph, and the rejections under 102 (e) and 103(a). The rejections are maintained for the reasons made of record in the office action mailed 8/10/07, and as follows.

Claims 1, 3-15, 17-19, 29-36, and 38-40 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for increasing production of IL-10 and decreasing INF-r and increasing T cell proliferation in an EAE animal model by administration of the IL-21 polypeptide of SEQ ID NO:2 to decrease the severity of symptoms that are regulated by inappropriate cytokine production, does not reasonably provide enablement for treating or ameliorating multiple sclerosis associated with an IL-10 deficiency, increased IFN-r by administering to a subject a structurally unknown agonist of IL-21/IL-21R as broadly claimed. In particular, at p. 13-15 of the response, Applicant argues that making and determining an agonistic anti-IL-21R antibody are routine. At p. 16-17 of the response, Applicant argues that amended claims are enabled because the specification provides support for treating or ameliorating MS or a symptome thereof based on the EAE mouse model. Applicant's arguments have been fully considered but they are not persuasive. In contrast, the claims are not limited to use of agonistic IL-21R antibodies. The claims encompass use of a genus of IL-21 polypeptides and use of a genus of agonistic anti-IL-21R antibodies. However, as previously made of record, the specification fails to provide sufficient guidance as to how to make the claimed genus of IL-21 polypeptides. In addition, although screening for an agonistic anti-IL-21R antibody that is generated from a defined sequence is routine, the claims are not limited to an antibody against a specific sequence of IL-21R. Further, the specification fails to teach what specific structures and sequences are requried for generating agonistic anti-IL-21R antibodies since the IL-21R polypeptide is not limited to a single amino acid sequence but also encompasses a genus of polypeptides that are not structurally and functionally defined by the specification. Furthermore, as previously made of record, the claims also recite treating which encompasses curing. However, neither the specification nor the prior art provides support to cure MS or its related symptoms by an agonist of IL-21/IL-21R. Thus, the instant invention is not enabled commensurate in scope with the claims or with the specification.

Claims 1, 29-30, 32-36 and 38-40 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. In particular, at p. 18 of the response, Applicant argues that the claims are limited to an IL-21 polypeptide with an example of SEQ ID NO:2, agonistic anti-IL-21R antibody or antigen-binding fragment of the agonistic anti-IL-21R antibody. As previously made of record, the recitation of IL-21 polypeptide in instant claims is not limited to SEQ ID NO:2 or 95% identity to SEQ ID NO:2. The specification defines "an IL-21 polypeptide" as including fragments of IL-21 and homologues with 30-95% identity to SEQ ID NO:2 on p. 18-20. However, the specification fails to teach what common structures and amino acid sequences are requried for the claimed genus of IL-21 polypeptides to be used in the claimed method. In addition, the specification fails to limit to IL-21R polypeptide and what sequence is required to generate an agonistic anti-IL-21R antibody. Thus, Applicant was not reasonably in possession of the “claimed genus of IL-21 polypeptides and the claimed genus of anti-IL-21R antibody and its antigen-binding fragments” that can be used in the claimed method.

Claims 17-19 and 34-40 stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite because of the recitation "IL-10 parameter". At p. 17 of the response, Applicant argues that the specification clearly describes the term "IL-10 parameter" at [0014] & [0028] comprising quantitative and qualtative information. Applicant's arguments have been fully considered but they are not persuasive. In contrast, the specification only describes examples to assay or evaluate IL-10 activity but fails to limit what specific parameter and activity of IL-10 are and would be within the scope of the claims. The disclosure fails to set forth the metes and bounds of what is encompassed within the definition of “an IL-10 parameter” and thus the claims are indefinite.

Claims 1,3-4, 9-12, 14 and 29-34 stand rejected under 35 U.S.C. 102 (e) as being anticipated by Novak et al. (US Patent No. 6605272, issued Aug 12, 2003, priority date Mar 9, 1999, as cited in IDS submitted May 23,2006). In particular, at p.20-21 of the response, Applicant argues that the '272 patent does not anticipate the claimed method and does not provide an enabling disclosure for such method. Applicant's arguments have been fully considered but they are not persuasive. In contrast, the '272 patent is enabling because an issued patent is an enabling disclosure. In addition, the ’272 patent does teach the claimed method of ameliorating MS symptoms by IL-21 polypeptides because the '272 patent teaches the same active step (i.e.administration of IL-21 as claimed) and material (i.e. IL-21 polypeptide), and the same patient population (i.e. MS). The '272 patent teaches a therapeutic use of IL-21 (ZALPHA11 ligand) in several immunological disorders including multiple sclerosis as recited in instant claims 1, 3-4, 9-12 and 29-34 (see col. 42, lines 9-31; col.192-198, claims 1-21, in particular). The limitation of ameliorating a symptom of MS or MS associated with an IL-10 deficiency or disorders caused by inappropriate production of cytokines would be an inherent result of regulating immune responses of T cell proliferation and cytokines productions by administration of IL-21 because the ’272 patent teach that IL-21 enhances proliferation of CD4+ T cells, CD8+ cytotoxicity T cells and Natural killer cells and regulating production of cytokines such as increasing IL-10 decreasing IFN-r to treat immunological disorders mediated by cellular immunity as recited in instant claims 1, 29, 34 (see col.99-102, examples 41-42). Thus, the '272 patent anticipates the claimed method recited in instant claims.

Claims 1,3-15,17-19, and 29-34 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Novak et al. (US Patent No. 6605272, issued Aug 12, 2003, priority date Mar 9, 1999, as cited in IDS submitted May 23,2006) in view of Carter et al. (US20030108549A, published Jun 12, 2003, priority date Oct 4, 2001) and Kawai et al. (Cell Immunol. 1996. 171:262-8). At p. 23 of the response, Applicant argues that the '272 patent does not associate IL-21 with the modulation of IL-10 or IFN-r or treating or ameliorating MS, the combination with the '549 publication and Kawai et al does not render the claimed method obvious. Applicant's arguments have been fully considered but they are not persuasive. As previuosly made of record, the ’272 patent does teach the limitation of the claims 1, 3-4, 9-12, 14 and 29-34 as set forth in the office action mailed 8/10/07 and above. Although the ’272 patent does not teach an agonistic anti-IL-21 antibody and an anti-inflammatory agent, the '549 publication teaches an agonistic anti-IL-21R antibody as recited in instant claims 1 and 5-6 (see p. 3 [0023], p.5 [0041]) and use of a combination of anti-inflammatory agent including IFN-1a/b and an IL-21/IL21R agonist to treat T cell-mediated diseases such as tumor as it relates to claims 7-8 (see p.3 [0024], p.5 [0039], [0040], [0208]). In addition, the ‘549 publication

also teaches that an IL-21/IL21R agonist enhances T cell proliferation and cytokine regulation, which relates to ameliorating a symptom of MS or disorders-associated with cytokines. Although the '272 patent and the'549 publication do not teach injection of IL-21 agonists into the CNS as recited in instant claims 13-15, Kawai et al. teach administering monoclonal antibodies that are against LFA-1 and ICAM-1 in EAE rat model by intracerebroventricular and intrathecal administration routes. Thus, the claimed method is obvious over the applied references.

Claims 1,3-15,17-19,29-36 and 38-40 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Novak et al. (US Patent No. 6605272, issued Aug 12, 2003, priority date Mar 9, 1999, as cited in IDS submitted May 23,2006), Carter et al. (US20030108549A, published Jun 12, 2003, priority date Oct 4, 2001) and Kawai et al. (Cell Immunol. 1996. 171:262-8) and further in view of Beebe et al. (Cytokine & Growth Factor Rev. 2002. 13: 403-12 as in IDS submitted on 05/23/06). In particular, at p. 24 of the response, Applicant argues that although Beebe teaches that the level of IL-10 is low in MS, it does not provide a nexus between IL-21 and treatment of MS to have a motivation and expectation of success in treating MS associated with IL-10 deficiency by adminstration of an agonist of IL-21/IL-21R. Applicant's arguments have been fully considered but they are not persuasive. As previuosly made of record, As previuosly made of record, the '272 patent does teach the limitation of the claims 1, 3-15,17-19, and 29-34 as set forth in the office action mailed 8/10/07 and above.The teachings of Beebe provide a motivation and expectation of success in evaluating the level of IL-10 in MS patients before and after treatment. Thus, it would have been obvious to a skilled artisan to ameliorate a symptom of MS regulated by inappropriate production of IL-10 and IFN-r by incorporating the teachings of Beebe et al. to measure/monitor the levels of IL-10 in MS patients while practicing the claimed method of the '272 patent, and '549 publication and Kawai et al. because a low level of IL-10 is found in MS and EAE, and the level of IL-10 increases after a successful treatment of MS patients.

/CYW/
3/6/08